

WHAT IS CLAIMED IS:

1. A method of sequencing a target nucleic acid with a plurality of nucleic acid probes, said probes having fewer bases than said target, comprising the steps of:
- 5 contacting said probes with said target;
 identifying a first probe that specifically hybridizes to said target;
 selecting a first set of extension probes that comprise
10 at least two of A, C, T, U, and G extensions of said first probe; and
 identifying one of said first set of extension probes that hybridizes specifically to said target more strongly than others of said first set of extension probes, whereby said one of said extension probes identifies a base in said target nucleic acid.
- 15 2. A method as recited in claim 1 wherein substantially all of said nucleic acid probes comprise n nucleotides, and wherein said extension probes comprise n-1 nucleotides of said first probe.
- 20 3. A method as recited in claim 1 further comprising the steps of:
- selecting a second set of A, C, T, U, and G extension probes that extend in a direction opposite of said first set of extension probes; and
25 identifying one of said second set of extension probes that hybridizes specifically to said target more strongly than others of said second set of extension probes, whereby said one of said second set of extension probes identifies a second base in said target nucleic acid.
- 30 4. The method as recited in claim 1 further comprising the step of:
- repeating said steps of selecting sets of extension probes and identifying extension probes five or more times.
- 35 5. The method as recited in claim 1 wherein said step of identifying further comprises the steps of:
- identifying single base mismatch probes, said single base mismatch probes comprising at least two of A, C, T, U, and G monosubstitutions of said first set of extension probes;
40 recording hybridization affinity data of said single base mismatch probes; and
 selecting one of said first set of extension probes as a correct extension of said first probe when said hybridization

affinity data conform to expected hybridization affinity data of said single base mismatch probes.

5 6. The method as recited in claim 5 wherein said expected hybridization data comprise:
 higher binding affinity for probe/target complexes with a mismatch at termini of said extension probes; and
 lower binding affinity for probe/target complexes with a mismatch at internal portions of said complexes.

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 7. The method as recited in claim 6 wherein:
 said hybridization data are normalized to a hybridization value for one of said extension probes; and
 said step of identifying comprises selecting one of
15 said extension probes having terminal single base mismatch probes that do not have normalized hybridization values higher than a normalized value of said one of said extension probes.

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 8. The method as recited in claim 1 wherein the step of
20 identifying comprises the step of selecting one of said set of extension probes that exhibits a higher binding affinity to said target than other extension probes.

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 9. The method as recited in claim 1 wherein said step of
25 identifying is conducted in an appropriately programmed computer.

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 10. A method of determining if a nucleotide sequence of a target nucleic acid is the same as a sequence of a first nucleic acid comprising:

30 contacting said target nucleic acid to a plurality of nucleic acid probes;

 determining the affinity of said target to probes identical to, but for a single base mismatch, of said subsequence; and

35 determining that said nucleotide sequence of said target is the same as said first nucleic acid if said affinity of said target to probes identical to but for a single base mismatch follows a predetermined pattern.

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40 11. The method as recited in claim 10 wherein said predetermined pattern comprises affinity of said single base mismatch probes normalized to affinity of a perfect complement of said subsequence.

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12. The method as recited in claim 11 wherein said affinity of single base mismatch probes are plotted as affinity versus mismatch position, and normalized to said affinity of a perfect complement of said subsequence.

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13. The method as recited in claim 10 further comprising the step of determining that said nucleotide sequence of said target is not the same as said first nucleic acid if said affinity of said target to probes complementary to single base mismatches does not follow a predetermined pattern.

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14. A probe array of nucleic acids, said probe array selected from all possible probes to comprise an exact complement to a target nucleic acid, and single base mismatches of said exact complement.

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15. A library as recited in claim 14 wherein said nucleic acid probes are of a length between about 8 and 15 bases.

16. A library as recited in claim 14 wherein said library is on a single substrate.

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17. A library as recited in claim 14 wherein said library comprises probes of n-bases or less, and wherein said library comprises less than 50% of all possible probes of n-bases.

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18. A library as recited in claim 14 wherein said library comprises probes of n-bases or less, and wherein said library comprises less than 10% of all possible probes of n-bases.

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19. A nucleic acid probe kit comprising a core nucleic acid probe, said core probe exactly complementary to a nucleic acid target, and selected A, C, T, U, and G single base substitutions of said core probe.

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20. A nucleic acid probe kit as recited in claim 19 consisting essentially of said core probe and A, C, T, and G single base substitutions of said core probe.

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21. A nucleic acid probe kit as recited in claim 19 further comprising instructions for determining if a target sample is the same as or different than said target.

22. A nucleic acid probe kit as recited in claim 19 wherein said core probe comprises between 8 and 15 bases.

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23. A nucleic acid probe kit as recited in claim 19 wherein said probes are selected to evaluate a target sample for a genetic characteristic selected from the group consisting of sickle cell anemia, P-53 mutations, cystic fibrosis mutations, HLA class 1 genes, and HLA class 2 genes.

24. A nucleic acid probe kit as recited in claim 19 wherein said probes are selected to evaluate a target sample for sickle cell anemia.